Amendments:

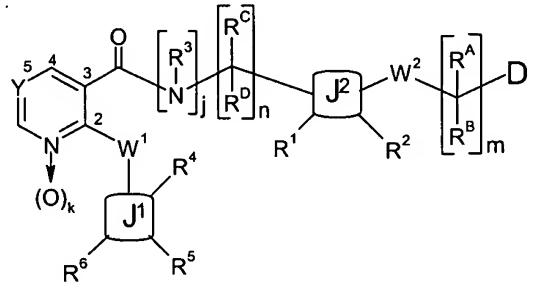
Entry of the above amendments and reconsideration and withdrawal of the rejection of claims is respectfully requested. Claims 1 and 4 were amended to remove language which was intended to be canceled in the first amendment sent March 27, 2003. Claim 25 was amended to delete compounds not within the scope of the elected group and to remove extraneous language which referred to the specification. All amendments were made without waiver or prejudice. Applicants reserve the right to file divisional or continuation applications directed to the nonelected or other canceled subject matter of this invention.

The Objection to the Claims:

The Examiner has objected to the claims, alleging that applicants have not fully conformed the claims to the elected group; that the method claims have not been amended to comprise allergy and respiratory diseases only; and that Claim 25 has not been amended to J^1 being a heterocyclic ring only since R^5 and R^6 may be combined to give a five membered ring.

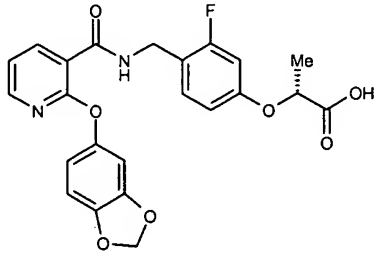
Applicants maintain that the method claims are directed only to respiratory ailments. Each of the diseases and conditions set forth in claims 31 - 40 are respiratory disorders, each of which is enabled by the specification (see below).

Applicants respectfully submit that the Examiner's objection that the claims have not been amended so that J^1 is only a heterocyclic ring be reconsidered and withdrawn. In a telephone conversation with the Examiner on November 21, 2002, Applicants' Attorney elected the compound of **Example 8**, which is Compound (5.5.8), found on page 97 of the specification. Example 8 is the compound of Formula (1.0.0),

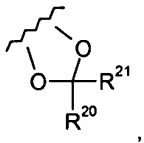


(1.0.0)

wherein Y is CH, k is 0, W^1 is O, J^1 is phenyl, R^4 is H, R^5 and R^6 are taken together to form a group of partial Formula (1.3.1) wherein R^{20} and R^{21} are each H, R^3 is H, j is 1, n is 1, R^C and R^D are each H, J^2 is phenyl, R^1 is F, R^2 is H, W^2 is O m is 1, R^A and R^B are each h and D is carboxy, having the following chemical structure:



Accordingly, Applicants submit that the Examiner's requirement to amend J^1 to be a heterocyclic ring is contrary to the elected species, around which the Examiner constructed a genus. Applicants submit that, in the above structure, *J^1 is phenyl* and *R^5 and R^6 are taken together to form*



where R^{20} and R^{21} are each H.

Applicants believe that the Examiner intended to require applicants to remove compounds from claim 25 which are not within the scope of the elected group and, additionally, of claim 1, as amended. Applicants have canceled the following compounds from claim 25: the compounds of Formula 5.5.3; 5.5.7; 5.5.10; 5.5.13; 5.5.15; 5.5.16; 5.5.30; 5.5.31; 5.5.32; 5.5.36; 5.5.37; 5.5.38; 5.5.42; 5.5.43; 5.5.44; 5.5.48; 5.5.49; 5.5.50; 5.5.53; 5.5.54; 5.5.55; 5.5.59; 5.5.60; 5.5.61; 5.5.65; 5.5.83; 5.5.84; 5.5.85; 5.5.89; and 5.5.97. Applicants respectfully request that the Examiner reconsider and withdraw the objection to claim 25, as amended.

The 35 U.S.C. §112, first paragraph, rejection.

The Examiner has rejected claims 31 - 40 under 35 U.S.C. §112, first paragraph, alleging that the specification, while being enabling for anti-allergic (sic) and asthma, does not reasonably provide enablement for any and all kinds of bronchitis, staphylococcus or streptococcal bronchitis. The Examiner has alleged that bronchitis may be treated with antibiotics rather than anti-allergents (sic). Applicants respectfully traverse.

Applicants respectfully submit that the specification enables the methods of treating all of the diseases, disorders and conditions set forth in claims 31 - 40. In the specification, at page 131, line 1 through page 142, line 17, Applicants clearly and in great detail set forth the basis for the claims directed to methods of treating respiratory diseases, disorders and conditions, i.e., claims 31-40.

Section 8.0 of the specification, beginning on page 131 and entitled "Therapeutic Applications and Clinical Endpoints," describes the therapeutic uses for which the compounds of the instant invention may be used. Therein, it is stated that "PDE4 is the major cAMP-metabolizing enzyme in ... inflammatory cells, and is one of two major cAMP-metabolizing enzymes in airway smooth muscle." (specification at page 132, lines 13 - 15) The compounds of Formula(1.0.0) of the instant invention inhibit PDE4 and, accordingly, are useful in treating diseases, disorders and conditions which are inflammatory in nature. This includes asthma, bronchitis, and any respiratory disorder wherein inflammation is involved, regardless of the trigger leading to the inflammation.

Section 8.1 of the specification, beginning on page 132, refers specifically to asthma. Therein it is stated that "[o]ne of the most important respiratory diseases treatable with PDE4, especially PDE4D inhibitors of the type within the scope of the compounds of Formula (1.0.0) is asthma." It is also stated that "asthma [is] a chronic, increasingly common disorder encountered worldwide and [is] characterized by intermittent irreversible airway obstruction, airway hyper-responsiveness and inflammation." The specification further states that the "cause of asthma has yet to be determined, but the most common pathological *expression* of asthma is *inflammation of the airways*. (specification at page 132, lines 31 - 35, emphasis added) Further, the specification discloses that "asthma involves infiltration by ...eosinophils ... into a patient's airways." (specification at page 132, line 37 to page 133, line 1) Finally, the specification discloses that the compounds of Formula (1.0.0) of the instant invention inhibit PDE4 in human eosinophils and are therefore useful in the treatment of both atopic and non-atopic asthma. "Atopic asthma" is defined in the specification as being synonymous with "allergic asthma." The term "non-atopic asthma" is intended to refer to *all other asthmas*. At page 133, line 17 to page 134, line 6 of the specification, Applicants describe an assay which demonstrates the reduction

of pulmonary inflammation in allergic cynomolgus monkeys by using the compounds of formula (1.0.0) of the instant invention. At page 134, lines 10 - 31 of the specification, Applicants describe an assay which demonstrates the anti-inflammatory activity of the compounds of the invention. Since PDE4 inhibition treats inflammation of the airways, which is the *expression* of asthma, the actual trigger causing the infiltration of eosinophils into the airways is irrelevant. Accordingly, Applicants submit that treatment of the various forms of asthma with a compound of Formula (1.0.0) is enabled by the specification.

Section 8.2 of the specification, beginning on page 136, refers specifically to chronic pulmonary obstructive disease and related disorders, including chronic bronchitis, chronic obstructive airways disease, pulmonary emphysema and dyspnea. (specification at page 136, lines 8 - 9) Therein it is disclosed that COPD is characterized by irreversible, progressive airways obstruction and that chronic bronchitis is associated with hyperplasia and hypertrophy of the mucus secreting glands of the submucosa in the large cartalaginous airways. (specification at page 9 - 12) Further, it is stated that COPD and asthma are each associated with inflammation of the airways, but that with COPD, the inflammatory cells are neutrophils rather than eosinophils. (specification at page 136, lines 24 - 26) It is further disclosed that the compounds of Formula (1.0.0) inhibit PDE4 in neutrophils, and that this results in reduced chemotaxis, activation, adherence, and degranulation. (specification at page 137, lines 12 - 18) At page 136, line 34, to page 137, line 19 of the specification, Applicants disclose references to numerous assays which may be used to demonstrate the ability of the compounds of Formula (1.0.0) to inhibit neutrophils. Accordingly, Applicants submit that the treatment of chronic bronchitis, chronic obstructive airways disease, pulmonary emphysema and dyspnea with a compound of Formula (1.0.0) is enabled by the specification.

Section 8.3 of the specification, beginning on page 138, refers specifically to bronchitis and bronchiectasis. Therein it is stated that the compounds of Formula (1.0.0) are useful in the treatment of acute bronchitis caused by various triggers including, *inter alia*, exposure to cold, irritant substances or an acute infection. (specification at page 138, line 23 to page 139, line 10. Bronchiectasis is also described at page 139, lines 11 to 25. At page 139, line 31 to page 140, line 8, Applicants describe an assay which demonstrates the ability of the compounds of Formula (1.0.0) to relax tracheal smooth muscle. Accordingly, Applicants submit that treatment of bronchitis with a compound of Formula (1.0.0) is enabled by the specification.

Section 8.4 of the specification, beginning on page 141, refers specifically to allergic and other forms of rhinitis and sinusitis. Therein, allergic and other forms of rhinitis are defined. (specification at page 141, lines 8 - 29) Sinusitis is defined at page 142, lines 9 - 17 of the specification. They are all defined as inflammatory diseases and as such are treatable by the compounds of Formula (1.0.0), since those compounds have been demonstrated to be useful in reducing inflammation. Accordingly, Applicants submit that treatment of allergic and other forms of rhinitis and sinusitis with a compound of Formula (1.0.0) is enabled by the specification.

The Examiner has alleged that treatment of bronchitis may be effected with antibiotics rather than with anti-allergents (sic). Applicants respectfully submit that the ability of compounds of other classes of drugs, e.g., antibacterials, to treat bronchitis is of no relevance to the ability of the compounds of the instant invention to treat bronchitis. In fact, using the Examiner's example, Applicants submit that antibacterials are not sufficient to treat bronchitis caused by bacteria. While the antibacterial may eradicate the bacteria, the effect of the bacteria on the airways, i.e., the inflammation caused by the intrusion of neutrophils, must still be treated before the symptoms of bronchitis disappear. As stated above, the ability of the compounds of the instant invention to treat any and all respiratory diseases, including any form of bronchitis, even bronchitis triggered by a bacterial infection, is demonstrated by the ability of the compounds of the instant invention to reduce inflammation in eosinophils and neutrophils.

In light of the disclosure made in the specification, Applicants submit that a person skilled in the art would readily appreciate that the compounds of Formula (1.0.0) are useful in treating all of the diseases, conditions and disorders set forth in claims 31 - 40. Accordingly, Applicants submit that all of the forms of asthma, bronchitis and other respiratory diseases and conditions set forth in claims 31 - 39 satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. Applicants respectfully request that the Examiner reconsider and withdraw the 35 U.S.C. §112, first paragraph rejection of claims 31 - 40.

The 35 U.S.C. §112, second paragraph, rejection.

The Examiner has rejected claim 25 under 35 U.S.C. §112, second paragraph, alleging that it is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that the claims are unclear due to the presence of formula numbers, which refer back to the specification. Applicants have amended claim 25 hereinabove to remove those numbers, rendering this rejection moot. Applicants respectfully request that the Examiner reconsider and withdraw the 35 U.S.C. §112, second paragraph, rejection of claim 25, as amended.

-Conclusion-

Applicants, having responded to all points and concerns raised by the Examiner, believe this application to be in condition for allowance. An early and favorable action is respectfully requested.

Dated: December 4, 2003

Respectfully submitted,

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